REMARKS

I. Claims in the Case

Claims 1-3, 6, 26-29, and 35-37 are canceled. Claims 7, 9, 30 and 32 are currently amended. No claims have been added. Claims 4, 5, 7-25, 30-34 and 38- 45 are pending, of which claims 11, 13-18, 20-21 and 24 are currently withdrawn.

II. Provisional Double Patenting

The Action first provisionally rejects various of the claims over various claims of later-filed copending application 10/261,078. In response to this rejection, Applicants note that the '078 application is still pending and no claims have been allowed. Thus, if the present case is in condition for allowance it is appropriate to withdraw the provisional double patenting rejection.

III. Rejection of Claims 4-8, 12, 25, 30-34 and 38-45 under 35 U.S.C. § 103

The Action next rejects claims 4-8, 12, 25, 30-34 and 38-45 as obvious over the combination of Zufferey *et al.* in view of Deisseroth.

In response, Applicants will limit their comments here to the two principal claims, claims 30 and 32, but reserves the right to further the separate patentability of various dependent claims should an appeal be necessary.

Turning first to claim 30, and claims depending therefrom, it is noted that this claim is now directed to the use of a promoter that is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 10 and about 200 in both a human hematopoietic progenitor cell and a differentiated hematopoietic cell. Of course, examples of such a promoter can be found in the list set forth in claim 9 (*e.g.*, EF1-α promoter, a PGK promoter, a gp91phox promoter, a MHC class II promoter, a clotting Factor IX promoter, a clotting Factor V111 promoter, an insulin promoter, a PDX1 promoter, a CD11 promoter, a CD4 promoter, a CD2 promoter or a gp47 promoter).

The Action curiously states that "the cited art teaches that inactivation of LTR provide higher signal to noise ratio which falls in the range of about 10 to about 200" referring to page 9876, Table 2, of the Zufferey *et al.* reference. We have carefully considered Table 2 of this reference and fail to see how that table in any way teaches or suggests the presently claimed subject matter. Indeed, Table 2 does not appear to include any data showing the background present in a control cell, so it could not reasonably be expected to teach or suggest a signal-to-noise parameter. Example 3 of the present specification sets forth one means of assessing signal-to-noise ratios, and defines signal-to-noise for the purposes of Example 3 to be "mean of fluorescence intensity of GFP+ cells divided by mean of fluorescence intensity of GFP- cells". Specification, page 57, lines 27-28. No such information, though, is set forth in Table 2 of the Zufferey *et al.* reference. Additionally, Table 2 of Zufferey *et al.* presents data from transductions with HeLa, HeLa-tat, and 293T cells lines which are cancer cells lines that express viral oncogenes. These cell lines are clearly <u>not</u> human hematopoietic progenitor or differentiated hematopoietic cells, nor are they representative of such cells.

Thus, for the foregoing reasons, the subject matter of claims 30 and dependents is in no way obviated by the cited references, alone or in combination.

Turning now to claim 32 and dependents therefrom, we would first note that a similar limitation has been introduced into that claim, which is now directed to the use of a promoter that is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 10 and about 200 in a differentiated hematopoietic cell. Claim 32 also now includes the further step of differentiating the transduced stem cell into a differentiated hematopoietic cell.

With respect to the "use of a promoter that is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 10 and about 200" we refer the Examiner to the arguments set forth above with respect to claim 30 and dependents.

With respect to the inclusion of the further step of differentiating the transduced stem cell into a differentiated hematopoietic cell, we have been unable to identify any teaching or suggestion of such a step in either of the cited references. If we are mistaken, the Examiner is respectfully requested to point out the teaching that is being relied upon for this aspect, as we have been unable to identify any discussion of this aspect in the Action, even though it is similar (but not identical) to the language of rejected claim 38.

For the foregoing reasons, the Examiner is requested to reconsider and withdraw this rejection.

IV. Rejection of Claims 6-10 Under 35 U.S.C. § 103

The Action next rejects claims 6-10 as obvious over the same combination, further in view of Chang *et al.*, which is said to teach lentiviral vectors incorporating an EF1-α promoter.

In response, Applicants first incorporate by reference the arguments set forth above with respect to claim 30.

Furthermore, it is our position that there is no motivation to combine the teachings of Chang *et al.* with those of Zufferey *et al.*, in that there was no reasonable expectation that the SIN design would work in hematopoeitic cells. We have been unable to identify any teaching *per se* in Zufferey *et al.* that would suggest to employ the SIN design in the context of hematopoietic cells, particularly hematopoietic progenitor cells. If the Examiner is aware of any such teaching she is respectfully requested to point it out. In fact, the SIN design incorporates modifications in their LTR region that reduces their promoter activity, and there was simply no way of knowing in advance what effect this would have on its ability to transfect and express in such cells. The reason for this is that neither the transcriptional milieu nor the specificities in hematopoietic cells, particularly hematopoietic progenitor cells, have been well characterized. As a consequence, the behavior of internal promoters with respect to the LTR regions in the

context of a SIN design could not be predicted in advance. Thus, without having a reasonable expectation that a SIN vector could be successfully employed in hematopoietic cells, there would be no reason or basis for modifying the SIN-CMV construct of Zufferey *et al.* Futhermore, Zufferey *et al.* not only fails to suggest the applicability of SIN design vectors to hematopoietic cells, it also appears to be silent as to any drawbacks associated with the CMV promoter in this or any context.

The Action apparently attempts to confront the foregoing argument by taking the position that Chang demonstrates that usefulness of the EF1-α promoter in a lentivector in the context of CD34+ cells. However, this is not precisely the case – the lentivector employed by Chang was NOT a SIN design, which as explained above can have a substantial effect on promoter behaviour and transgene expression, and thus there is no way to predict in advance of the present application that promoters taught be Chang could be used advantageously in the context of the SIN design. Additionally, Chang fails to demonstrate whether the EF1-α promoter would remain active in differentiated hematopoietic cells, which would not have been clear to one of skill in the art at the time the invention was made. In contrast, the inventors demonstrate that when hematopoietic progenitor cells are transduced by vectors comprising the EF1-α promoter and then differentiated "transgene expression was high in all lineages examined after transduction" (see page 57 lines 23-29 of the specification). This result would clearly have been obvious to one of skill in the art, since as pointed out in the specification, other promoters (*e.g.* CMV) are "only minimally active in most progenitor cells" (page 6 lines 17 – 19). Thus, at the time of invention it would have been unclear to one of skill in the art that there was any advantage to using the EF1-α promoter, especially in the context of a SIN vector.

Accordingly, a *prima facie* obviousness rejection has not been properly set forth.

V. Rejection of Claims 19, 22 and 23 Under 35 U.S.C. § 103

The Action next rejects claims 19, 22 and 23 over Zufferey *et al.* in view of Deisseroth and further in view of Zufferey *et al.* (1999).

In response, Applicants incorporate by reference the arguments set forth above with respect to claim 30, from which Claims 19, 22 and 23 depend.

VI. Rejection of Claims 6-8 Under 35 U.S.C. § 112, Second Paragraph

Lastly, the Action rejects claims 6-10 and 29-37 under 35 U.S.C. §112, second paragraph, for various reasons as discussed below.

First, 6-8 and 31 are rejected due to their use of the phrase "about." The Action contends that "about" means "reasonably close or in the vicinity" and thus is not sufficiently clear when used in the context of defining a signal-to-noise ratio.

Applicants respectfully disagree, and again direct the Examiner's attention to MPEP 2173.05(b) and particularly the section labeled "About". This section, and the cases cited therein, make it clear that the use of the phrase "about" does not render a claim improper under section 112, second paragraph, unless there is close prior art with respect to the particular limitation and that that limitation is critical to distinguishing the invention. Furthermore, it is noted that the term "about" has been interpreted by at least one court in a biotechnology case to mean within the standard error of the measurement technique. See, *e.g.*, *Hybritech Inc. v. Abbott Laboratories*, 4 U.S.P.Q.2d 1001, 1013 (C.D.Cal. 1987), *aff'd*, 849 F.2d 1988 (Fed. Cir. 1988). Applicants respectfully request that the Examiner reconsider and withdraw the rejection as to these claims.

The Action's response to the foregoing argument is that in *Amgen*, according to the Examiner, the CAFC held that claims reciting "at least about" invalid for indefiniteness where there was close prior art. We have reviewed the Amgen case and find that it is inapplicable here.

First, the claim term here goes to the question of what constitutes an appropriate promoter. There has been no question on this record about whether or not a particular promoter falls within this language, so there is no question here about "close prior art" that is impacted by this particular parameter. Moreover, the *Amgen* court actually recognized that the term "about" is typically an acceptable term, and further noted that the claims at issue there would have been invalid even if they didn't include the "about" term. *Amgen*, 18 USPQ2d at 1031.

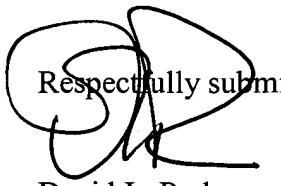
The remaining case cited by the Examiner, *Ex parte Oetiker*, is submitted to be irrelevant to our facts in that *Oetiker* turned on the fact that the specification there failed to apprise those of skill how to make the measurements at issue. This is not the case here, where a specific procedure has been provided in Example 3 for carrying out the claimed signal-to-noise ratio. In light of the holding in Abbott that the word "about" means within the standard error of the technique employed to make the measurement, and further in light of the fact that the specification teaches a useful method for making such a measurement, one of skill would certainly understand the meaning of the term "about" in the rejected claims.

For each of the foregoing reasons, the Examiner is respectfully requested to reconsider and withdraw the section 112, 2nd paragraph, rejection.

VII. Conclusion

It is submitted that the present case is now in condition for allowance, and a favorable action is earnestly solicited. In this regard, the Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



David L. Parker
Reg. No. 32,165
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: August 24, 2004